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ARAŞTIRMA / RESEARCH

Efficacy of magnetic resonance imaging as a tool to assess central nervous system involvement of COVID-19

COVID-19'un santral sinir sistemi tutulumunu değerlendirmek için bir araç olarak manyetik rezonans görüntülemenin etkinliği

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Abstract

Purpose: The aim of this study was to identify patients with acute neurological findings associated with COVID-19 and to demonstrate the effectiveness of magnetic resonance imaging (MRI) in its diagnosis.
Materials and Methods: Between June 2020 and December 2021, 90 patients who were diagnosed with Covid-19 in our clinic, had pneumonia findings in the lung, acute neurological findings, and brain MRI were included in the study. Results were evaluated retrospectively for 46 patients without central nervous system (CNS) involvement and 44 patients with CNS findings.
Results: The most common neurological symptoms in COVID-19 patients; Unexplained loss of consciousness by treatment (28/44, 63.6%), focal neurologic deficits (21/44, 47.7%), and seizures (9/44, 20.4%). Increased mortality, increment in the need for ventilator support, and prolonged stay in the intensive care unit were observed in patients with CNS findings. Brain MRI was performed on 44 patients with neurological symptoms. Mean age of 68.3 years (45–78) in patients undergoing MRI. Acute findings were detected in MRI of 32 patients (72%). The most common diagnoses in brain MRI were acute and subacute infarcts.
Conclusion: The mechanism of CNS manifestations is still unclear, and neurological symptoms in COVID-19 patients are an important problem, especially in intensive care units. Therefore, early detection and treatment of CNS involvement are very important.
Keywords:. Covid-19, confusion, central nervous system, MRI

Öz

Amaç: Çalışmamızın amacı, COVID-19 ile ilişkili akut nörolojik bulguları olan hastaları tanımlamayı ve tanısında manyetik rezonans görüntüleme (MRG) etkinliğinin gösterilmesini amaçlamaktır.
Gereç ve Yöntem: Haziran 2020 ve Aralık 2021 tarihleri arasında kliniğimizde Covid-19 tanısı almış, akciğerde pnömoni bulguları olan, akut nörolojik bulguları olan ve Beyin MRG olan 90 hasta çalışmaya alındı. Bulgular santral sinir sistemi (SSS) tutulumu bulgulari olmayan 46 hasta ve SSS bulgulari olan 44 hasta retrospektif olarak değerlendirildi.
Bulgular: COVID-19 hastalarında en sık görülen nörolojik belirtiler; tedavi ile açıklanamayan şuur kayıbı (28/44, %63,6), focal nörolojik defisit (21/44, %47,7) and nöbet (9/44, %20,4). SSS tutulumu olan hastalarda yoğunbakımda yatış sürelerinde uzama, ventilator desteği gereksinimde artış ve mortalitede artış görüldü. Nörolojik semptomları olan 44 hastaya beyin MRG çekildi. MRG çekilen hastalarda 68,3 ortalama yaş (45–78). 32 hastanın (%72) MRG'nda akut bulgular saptandı. Beyin MR görüntülemesinde en sık konulan tanılar akut ve subakut infarktlardı.
Sonuç: Merkezi sinir sistemi bulgularının mekanizması hala belirsizdir, COVID-19 hastalarında nörolojik semptomlar özellikle yoğun bakım ünitelerinde önemli bir sorundur. Bu nedenle SSS tutulumunun erken tespiti ve tedavisi çok önemlidir.

Anahtar kelimeler: Covid-19, konfüzyon, santral sinir sistemi, MRI

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INTRODUCTION

Since its first diagnosis in December 2019, COVID-19 has resulted in more than 120 million cases and 2.6 million deaths. Many people infected with COVID-19 are asymptomatic. While patients predominantly experience respiratory symptoms, neurological symptoms and conditions are increasingly recognized[1-3].

The virus enters using angiotensin-converting enzyme 2 (ACE-2) receptors. It causes inflammation in endothelial cells, causing thrombus and brain damage[4]. The inability to smell and taste is characteristic of COVID-19, suggesting a possible pathway for the olfactory nerve to enter the central nervous system (CNS)[5,6]. Other neurological findings such as headache, myelopathy, encephalopathy, and Guillain-Barre syndrome are rarely seen[3,7].

Diagnosis of COVID-19 pneumonia can be made by commonly reported imaging features, bilateral diffuse peripheral ground-glass opacities with areas of consolidation in high-resolution computed tomography of the lung (HRCT) scan. However, in patients with central nervous system involvement with neurological symptoms, brain CT is usually normal in the early period. In the early period of brain involvement, imaging features with high signal intensity are seen in brain magnetic resonance imaging (MRI) in the areas with involvement in FLAIR images.

Neurological manifestations of COVID-19 infection are increasingly being reported and include cerebrovascular complications, leukoencephalopathy, and other CNS disorders. However, the question is whether COVID-19 will cause neurological diseases. Whether it occurs through a direct neuropathic effect or by activating the hyperinflammatory reaction and causing cytokine release syndrome (CRS) by the host's immune system is not yet understood[8].

Diagnosis remains challenging due to the severity of respiratory and systemic manifestations accompanying neurological symptoms in COVID-19 patients. The use of MRI in COVID-19-associated encephalopathy has not been well explained in the literature to date. This study aims to identify patients with acute neurological findings and functional abnormalities associated with COVID-19 and to demonstrate the effectiveness of MRI in its early diagnosis.

MATERIALS AND METHODS

Study population

Between June 2020 and December 2021, 90 patients who were diagnosed with Covid-19 in Medical Park Mersin Hospital and Corlu state Hospital were included in this retrospective study. The clinical course, neurological findings, laboratory data, and neuroimaging findings were reviewed retrospectively using a structured research form. For our study, approval no. 772.02-5618 was received by İstanbul Medipol University on November 3, 2021, and was carried out under the Declaration of Helsinki. Written informed consent was obtained from all participants.

Patient selection

Inclusion criteria were: 1) Age over 18, 2) having brain MRI, 3) Detection of RNA from the nasopharyngeal filtrate, reverse-transcriptase–polymerase-chain-reaction (RT-PCR) from bronchial lavage or Covid- 19 pneumonia in HRCT scan 4) acute neurological symptoms. As exclusion criteria: 1) Patients without enough data 2) Taking neuromuscular blocking medication during hospitalization 3) Patients with progressive CNS disease other than stroke 4) Recent history of head injury were excluded.

Data collection

Clinical information, laboratory results, and radiological findings were obtained retrospectively from hospital electronic medical records. Symptoms, demographical information, comorbidities, and neurological findings by three experienced neurosurgeons.

Patients were scanned using a 1.5 Tesla MRI system (SIGNA, General Electric Healthcare). Diffusion-weighted imaging, apparent diffusion coefficient (ADC), T1WI, T2WI, fluid-attenuation-inversion-recovery (FLAIR), and susceptibility-weighted imaging (SWI) images were obtained.

The findings of patients in intensive care units (ICU) and other departments (outside ICU) were analyzed separately. All patients received a combination of supportive therapy and an antibiotic/antiviral agent combination. The patient was given additional treatment for his additional disease (cerebrovascular disease, diabetes mellitus, hypertension, etc.).

Mechanical ventilatory support was provided to patients with severe respiratory distress.

Statistical analysis

In comparisons between the two study groups; Student's t-test was used for Gaussian continuous variables, Categorical variables are described as numbers and proportions and were compared using Pearson's χ2 tests or Fisher's exact tests depending on theoretical numbers. Comparisons of the mechanical ventilation duration and ICU length of stay were performed using a multivariable gamma regression model. An adjustment was realized on the potential confounding factors (age, sex, neurological medical history, and chronic diseases). All analyzes were considered with R software V.3.3.2 and *the P<0.05* level was considered significant.

RESULTS

90 patients diagnosed with Covid-19 were included in the study. The mean age was 63.6 (66.6% male). Common symptoms at admission were fever, cough, and dyspnea. The duration of neurological symptoms after the onset of COVID-19 symptoms was 6.1 days (range: 0-20). The most common neurological symptoms were; loss of consciousness unexplained by treatment (28/44, 63.6%), focal neurologic deficit (21/44, 47.7%), and seizure (9/44, 20.4%). The demographic characteristics of the patients are shown in Table 1.

Table 1. Demographic characteristics of the patients.

	Total (n=90)	Covid-19 (n=46)	CNS+ Covid-19 (n=44)
Mean age (y)*	63.6 (23–78)	57.1 (23–74)	68.3 (45–78)
Male sex, n (%)	60 (66.6)	29 (65.9)	31 (70.4)
Risk factor, n (%)	HT (n = 51); DM (n = 39); CAD (n = 19); CVD (n = 16); CKD (n = 5); lung cancer (n = 1)	HT (n = 27); DM (n = 20); CAD (n = 7); CKD (n = 1)	HT (n = 24); DM (n = 19); CVD (n = 16); CAD (n = 12); CKD (n = 4); lung cancer (n = 1)
Time from symptom onset to ICU admission (d)*	3 (0–6)	4(0–6)	2 (0–3)
Intubation	46	16	29
Noninvasive ventilator support	23	7	16
Length of ICU stay (days)	14	8	17
ICU mortality—n (%)	25 (56.8)	7(15.9)	18 (40.9)

RD = Respiratory disease, CAD = coronary artery disease, CKD = chronic kidney disease, COVID-19 = coronavirus disease 2019,; CVD = cerebrovascular disease DM = diabetes mellitus, HT = hypertension, ICU = intensive care unit.; * Numbers in parentheses are the minimum and maximum range.

There was a significant difference between inpatients and outpatients in the intensive care unit in terms of loss of consciousness (82.7% vs. 14.7%, *p<0.001*), but no significant difference was found in terms of focal neurologic deficit and seizures. 25 patients (56.8%) died during hospitalization. While 21 patients required non-invasive mechanical ventilator support, 46 patients required invasive mechanical ventilator support. A statistically significant difference was found between these two groups *(P<0.05).*

Brain MRI was performed on 44 patients with neurological symptoms. Mean age of 68.3 years (45–78) in patients undergoing MRI. Acute findings were detected in MRI of 32 patients (72%). Cortical FLAIR MRI scans of 13 (40%) of 32 patients showed abnormal signal intensity. Hemorrhage was detected in 9 (21%) patients. Subcortical and deep white matter signal intensity abnormality was observed in FLAIR MRI sections of 4 patients (Figures 1).

In brain MRI, abnormalities were detected in the frontal lobe in 10 patients, parietal lobe in 8 patients, occipital lobe in 10 patients, temporal lobe in 3 patients, insular cortex in 7 patients, and cingulate gyrus in 7 patients. Acute transverse sinus thrombosis was found in one patient and acute infarct due to thrombosis in the left middle cerebral artery was found in one patient.

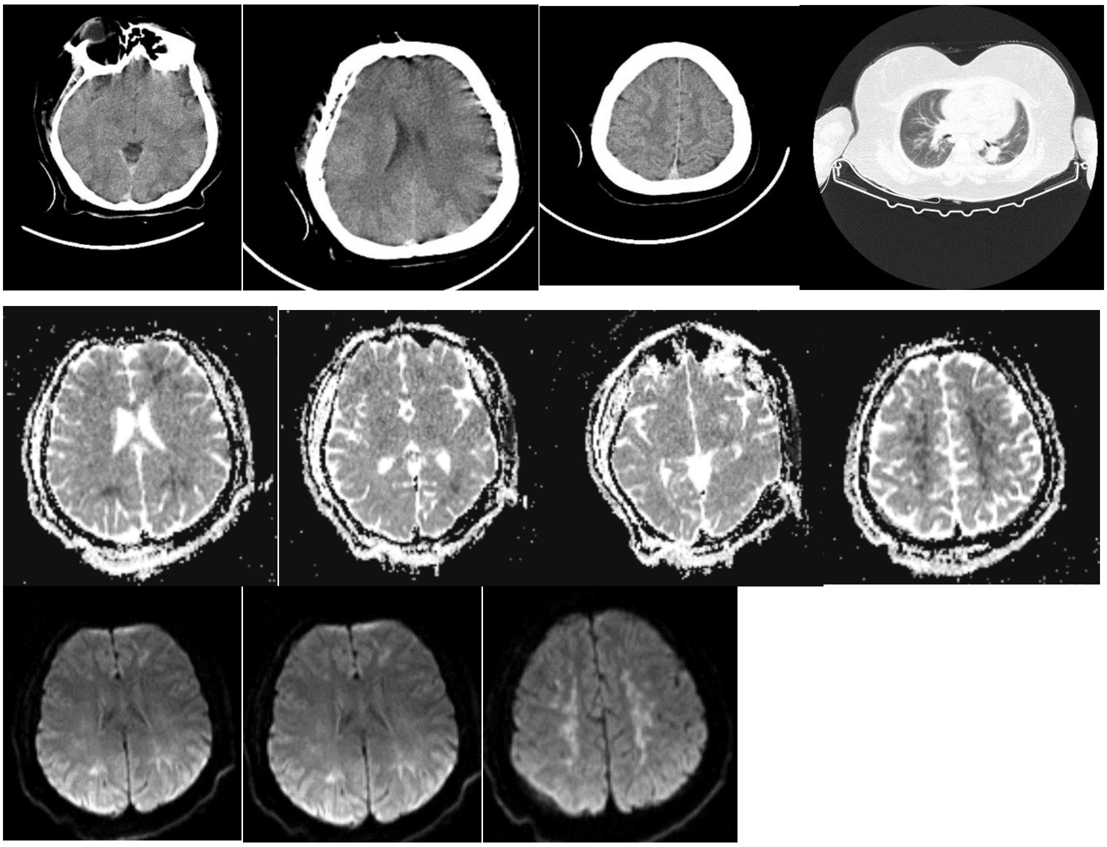

Figure 1. 23-year-old female patient. Bilateral diffuse peripheral ground-glass opacities with areas of consolidation in high-resolution computed tomography of the lung (HRCT) scan. Brain CT is normal. Normal Beyin CT. However, MRİ with deep white matter signal intensity abnormality.

Cortical signal changes in MRI were detected in 5 of 11 patients who underwent cerebrospinal fluid (CSF) analysis. Elevated total protein levels were detected in 4 of 5 patients (mean, 81.9 mg/dL; range, 62.9–108.7 mg/dL). Glucose, albumin level, immunoglobulin G level, and cell count were within normal limits. High protein levels were detected in the CSF of 3 of 12 patients with neurological symptoms but without acute findings in COVID-19 MRI (mean, 94 mg/dL). Negative results were obtained in the results of the COVID-19 test performed on the CSF of all patients.

DISCUSSION

İn many published articles, the most common imaging finding in COVID-19 is acute or subacute infarcts **(**Figures 2). In hospitalizations, acute stroke emerges as a very strong prognostic factor[9]. Acute stroke is most commonly encountered as acute intracranial hemorrhage, acute cerebrovascular diseases, acute ischemic stroke, and occlusion of great vessels[10,11]. Although this situation is thought to be due to thrombosis in vessels due to inflammation, platelet activation, and endothelial damage in COVID-19[12], the pathophysiology of stroke is still poorly understood. With the ongoing pandemic and further studies of COVID-19 disease, there is evidence that the neurological complications of COVID-19 disease are due in part to the cytokine storm[8,13]. Endothelial damage may develop due to high inflammation and cytokine release, and encephalopathy may be associated with changes in the blood-brain barrier[14,15]. For example, it is unclear whether the thrombosis occurs in a small artery, a large artery, or is due to vascular stenosis (for example atherosclerosis). Failure to detect virus RNA in CSF, increased protein levels, increased permeability in contrast-enhanced MRIs, and CRS[8,16] support an autoimmune event.

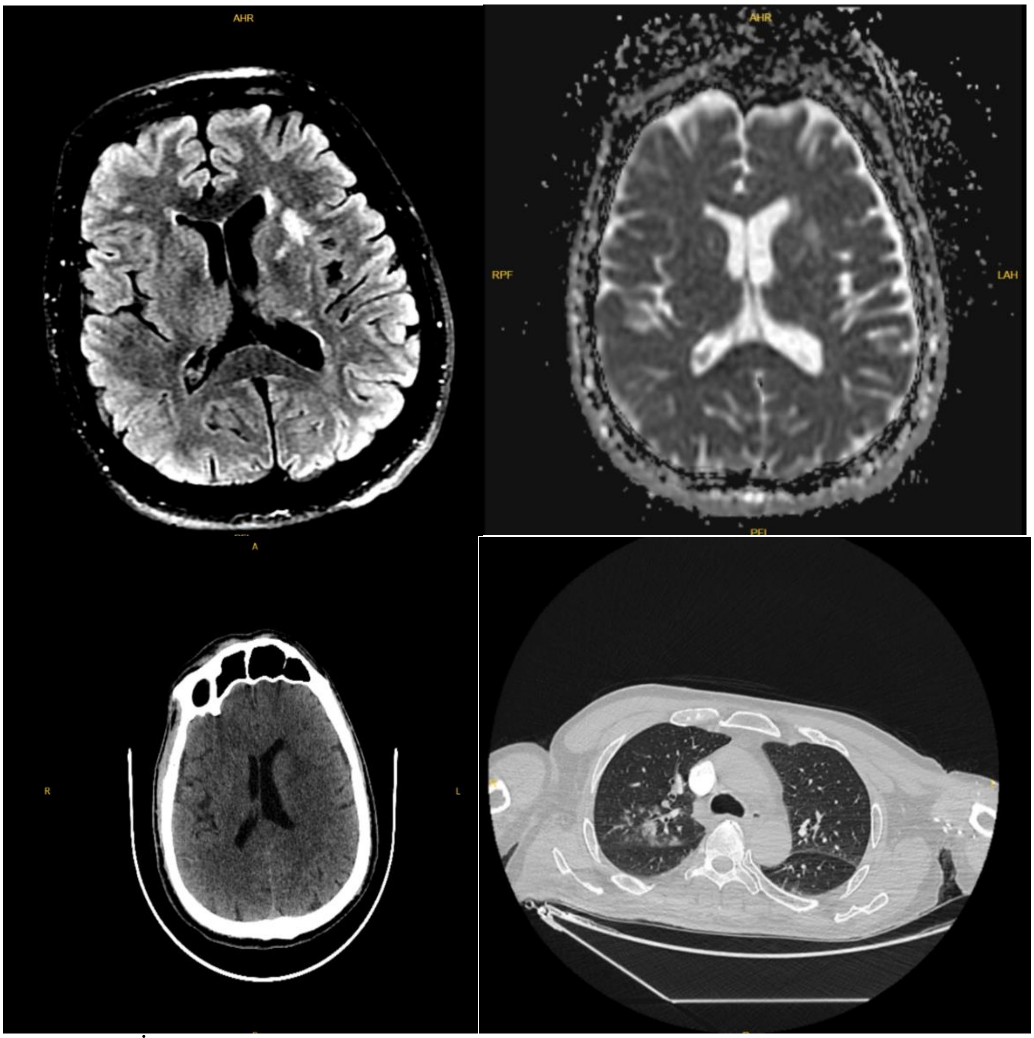

Figure 2. MRİ with finding in COVID-19 is acute or subacute infarcts

Neuroradiological imaging is not performed in patients with COVID-19 when clinical findings such as headache, seizure, and mental status change are not present. When done, Brain CT is preferred for its convenience. MRI is typically characterized by vasogenic encephalopathy[17].

In our study, we obtained a high rate of confusion and/or neurological symptoms in patients hospitalized in the intensive care unit due to respiratory distress because of COVID-19. This situation required us to give high-dose sedative drugs to patients and invasive mechanical ventilator support. As a result, the length of stay of the patients in the intensive care unit was prolonged. Patients were at increased risk of additional infections. In our study, the mortality rate between the patients who were treated in the intensive care unit and those treated in other services was statistically significant ($P<0.001$), (40.9% vs. 15.1%). It is thought that COVID-19 mostly affects men[18,19] due to the elevation of ACE-2 receptor cells in the lung[4,19]. This can also explain the high rate of men with confusion in the intensive care unit.

Hypoglycemia, hypoxia, and autoimmune encephalitis should be evaluated in the differential diagnosis[20,21]. Helms et al.[22]showed that hypoxia is involved in the pathogenesis of bifrontal and frontotemporal hypoperfusion in their study of COVID-19 in the intensive care unit. Perfusion abnormalities are most frequently observed in the temporal region and less frequently in the frontal region in the literature[10,22]. The reason why our results were different from the literature may be due to the small sample size in our study.

Although the restricted diffusion rates of patients with encephalopathy due to COVID-19 appear to be the same as patients with encephalopathy without COVID-19, the hemorrhage rate is higher. In some studies, hemorrhage was reported as 36% in patients with COVID-19, but in a more recent study, it was reported as 64.5%[23-25]. However, in our study, hemorrhage was detected in only 9 (21%) patients on MRI. It resulted in a limitation for our study.

The limitations of the current study are its retrospective nature, the small sample size, and the lack of standardization of indications across hospitals. The main strength of our work is to highlight emergencies. In patients with neurological findings, brain tomography is performed during admission to the emergency department due to the difficulty of getting a brain MRI. Unfortunately, tomography is usually found to be normal. The diagnosis of CNS involvement is ruled out and the diagnosis, treatment, and hospitalization periods of the patients are prolonged. This study may help to increase the awareness of possible neurological diseases and help to diagnose especially in the patients who cannot tolerate extubation despite their recovery in the intensive care unit.

In concluion, neurological complications associated with COVID-19 are still poorly understood. Although the neurological symptoms seem to be related to the systemic inflammatory reaction due to COVID-19, it requires further research for the pathophysiological mechanisms. COVID-19'a bağlı ensefalopatili hastalarda, COVID-19'u olmayan ensefalopatili hastalara göre daha yüksek kanama oranlarına sahiptir. A timely understanding of the relationship between the CNS and COVID-19 infection has great importance for the necessary approach to the disease.

Yazar Katkıları: Çalışma konsepti/Tasarımı: RA, MG; Veri toplama: RA, MG, CS; Veri analizi ve yorumlama: RA, MG, CS; Yazı taslağı: RA, MG, CS; İçeriğin eleştirel incelenmesi: RA, MG, CS; Son onay ve sorumluluk: RA, MG, CS; Teknik ve malzeme desteği: MG; Süpervizyon: CS; Fon sağlama (mevcut ise): yok.
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